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EXAMINER	
GREENE, JAIME M	
ART UNIT	**PAPER NUMBER**
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/549,252	BAI ET AL.	
	Examiner	Art Unit	
	Jaime M. Greene	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7* is/are pending in the application.

4a) Of the above claim(s) *4-7* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to papers filed 11/1/07. Claims 1-7 are pending and claims 1-3 are under examination on the merits.

Election/Restrictions

2. Applicant's election with traverse of Group I in the reply filed on 11/1/07 is acknowledged. The traversal is on the ground(s) that the sequences are obtained by sequencing the p16 gene. This argument has been found persuasive, and as such Groups I-IV have been rejoined. Therefore, claims 1-3, including SEQ ID NOs 1-4 will be examined on the merits.

3. The traversal is also on the ground(s) that the sequences are artificial sequences and therefore are not known in the prior art. This is not found persuasive because Groups I-IV only require a sequence complementary to a part of one of SEQ ID NOs: 1-4, and at least one such sequence is known in the prior art; see Belinsky (Belinsky, et al. US PGPub 20040038245, published 2/26/04, priority date 8/25/00), which is described further in the 102 rejection below. Also, since the methods only require a sequence complementary to a part of one of SEQ ID NOs: 1-4, there is no common special technical feature between the methods and products.

Therefore, the requirement for restriction between the method (Groups I-IV) and product (Groups V-VIII) claims is still deemed proper and is therefore made FINAL.

4. Claims 4-7 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or

linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 11/1/07.

Claim Objections

5. Claim 2 is objected to because of the following informalities: the word "malignat" in line 1 appears to be misspelled. Appropriate correction is required.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-3 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

8. The term "malignant potential" in claims 1-3 is a relative term which renders the claims indefinite. The term "malignant potential" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

9. Claims 1-3 are indefinite. The claims do not recite the basic steps of the claimed invention in a positive, active fashion (see Ex parte Erlich 3 USPQ2d, 1011). The claims describe a method for in vitro detection of malignant potential of dysplasia, but the claim fails to recite any actual steps that define the method. The limitation (e.g.

claim 1) that the procedure involve "extraction of genomic DNA from cells in a sample of tissue or body liquids" is not considered to meet the requirements of positive process steps because, since the claim is written in the passive tense, no guidance is given as to how to the extract the DNA. Claim 2-3 depend from claim 1 and are therefore similarly vague and indefinite.

Claim Rejections - 35 USC § 112 Written Description

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 1-3 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-3 are drawn to a method of in vitro detection of malignant potential of dysplasia comprising extracting genomic DNA from any sample, detecting the methylation state of p16 CpG islands in genomic DNA by amplification; and determining malignant potential of any sample based upon the presence of methylated p16 CpG. Since the claims are drawn to extracting DNA from cells in a sample of tissue or body liquid, the claims read on samples from any organism.

In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described

by their complete structure. In the instant case, the specification teaches sequences for identifying human p16 methylation. However, the claims read on a sample from any organism, and yet the specification does not provide any sequence information for non-human organisms.

Next, then, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (i.e. other than by name and functional characteristics), specific features and functional attributes that would distinguish different members of the claimed genus. In the instant case, the specification teaches sequences p16 methylation and the specification teaches sequences that can be used to detect human p16 methylation. The specification also cites a study on p16 hypermethylation in the Wistar rat (pg 6, para 18). The specification does not teach sequences for detecting p16 methylation in any other organism. However, a search of the prior art indicates that p16 methylation has also been studied in mice (See, e.g. Patel, et al. Carcinogenesis. 2000 Sep;21(9):1691-700, described further in enablement rejection below). Therefore, while the identifying information provides description for p16 methylation in humans, mice and rats, the specification does not provide description for p16 methylation in other organisms.

Applicants' attention is directed to the decision in In re Shokal, 113 USPQ 283 (CCPA 1957) wherein is stated:

It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. In re Soll, 25 C.C.P.A. (Patents) 1309, 97 F.2d 623, 38 USPQ 189; In re Wahlforss et al., 28 C.C.P.A. (Patents) 867, 117 F.2d 270, 48

USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as the halogens, consisting of four species, a reduction to practice of three, or perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary.

Also, Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

In the instant application, since the specification and the prior art do not provide any identifying information regarding sequences from organisms other than humans, mice, and rats, one of skill in the art cannot envision the detailed structure of the methylation state of p16 CpG islands in organism other than humans, mice and rats.

Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc.,

107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966.

An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. Fiers v. Revel, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id. at 1170, 25 USPQ2d at 1606.

The lack of information regarding the methylation sequence of p16 in any organism other than humans, mice and rats is not deemed sufficient to reasonably convey to one skilled in the art that Applicant is in possession of a method of in vitro detection of malignant potential of dysplasia comprising extracting genomic DNA from any sample, detecting the methylation state of p16 CpG islands in genomic DNA by

amplification; and determining malignant potential of any sample based upon the presence of methylated p16 CpG.

Thus, having considered the breadth of the claims and the provisions of the specification, it is concluded that the specification does not provide adequate written description for claims 1-3.

Claim Rejections - 35 USC § 112 Enablement

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claims 1-3 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with information known in the art without undue experimentation (*United States v. Teletronics Inc*, 8 USPQ2d 1217 (Fed Cir. 1988)). Whether undue experimentation is needed is not based on a single factor, but rather a conclusion reached by weighing many factors (See *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986)) and *In re Wands* 8 USPQ2d 1400 (Fed. Cir. 1988)).

<u>The breadth of the claims and nature of the invention</u>

Claims 1-3 are broadly drawn to a method of in vitro detection of malignant potential of dysplasia comprising extracting genomic DNA from any sample, detecting the methylation state of p16 CpG islands in genomic DNA by amplification; and determining malignant potential of any sample based upon the presence of methylated p16 CpG.

The nature of the invention not only involves determining the methylation of p16 CpG islands, but also using that information to determine malignant potential. Since the claims are drawn to extracting DNA from cells in a sample of tissue or body liquid, the claims read on samples from any organism.

Guidance in the Specification and Working Examples

The specification teaches that gastric biopsy samples of dysplasia that either progressed to gastric carcinoma or that persisted as dysplasia during a 5-year follow-up were studied (pg 10, para 32). The specification teaches performing MSP on the p16 CpG islands (pg 10, para 35 to pg 12, para 45), and the specification teaches that aberrant p16 methylation was observed in 5 of 21 samples of dysplasia that progressed to gastric carcinoma (24%). Therefore, aberrant hypermethylation is cannot predict with any significance the likelihood that a dysplasia will progress to gastric carcinoma.

The specification does not teach a means of determining malignant potential. The specification does not a means for distinguishing the malignant potential of dysplasia between patients who exhibit p16 methylation. The specification does not teach performing the experiment in other tissues. The specification does not teach studies performed in other organisms. Also, the specification does not teach a definition

for malignant potential of dysplasia, and therefore, the method broadly encompasses detection of cancer.

The unpredictability of the art, the state of the prior art, level of skill in the art

While the state of the art and level of skill in the art with regard to correlating gene expression with disease state is high, the level of unpredictability in associating any gene expression levels with a particular disease state is even higher. The level of unpredictability is demonstrated by the prior art, the post filing art, and the instant specification.

With regard to p16 methylation and detection of malignant potential of dysplasia, the art teaches several studies that associate p16 methylation and cancer. Bai (Bai, et al. Mutation Research 2003; 535:73–78) teaches that p16 promoter hypermethylation was observed during the process of neoplastic progression in rat gastric carcinoma (pg 77, col 1, para 2), Wong (Wong, et al. Cancer Research, January 1, 1999; 59;71–73) teaches detecting p16 methylation in the plasma or serum of HCC (hepatocellular carcinoma) patients (pg 71, col 1, introduction). Belinsky (Belinsky, et al. US PGPub 20040038245, published 2/26/04, priority date 8/25/00) teaches that p16 aberrant methylation was detected in 48% of patients with Squamous Cell Carcinoma (SCC). However, only Sun (Sun, et al. Clin Cancer Res, 8/1/04; 10:5087-5093) teaches a similar study on gastric dysplasia samples in which 5 of 21 patients who progressed to gastric carcinoma had methylated p16 (pg 5089, results). Sun also teaches that aberrant p16 methylation has been observed in dysplasia of the cervix, esophagus, lung and oral mucosa, but that aberrant p16 methylation was reported as being unable to

predict the evolution of precancerous bronchial lesions in a 2 year follow-up (pg 5089, col 2, para 2). Therefore, based on the art, it is unpredictable to use p16 methylation levels as a means of detecting malignant potential of dysplasia.

With regard to associations between methylation and cancer, Das (Das, et al. Journal of Clinical Oncology, 2004; 22(22):4632-4642) teaches that although certain genes such as RASSF1A and p16 are commonly methylated in a variety of cancers, other genes are methylated in specific cancers (page 4634, column 2, paragraph 1), suggesting that a correlation between methylation and one type of cancer cannot necessarily be extrapolated to all cancers. Das also teaches that the sensitivity and specificity of DNA methylation markers in cancer diagnosis depends on several factors, including the type of cancer and the gene to be studied, the type of body fluid to be used, and the technique involved, and that the assay needs to be standardized and shown to be useful in a prospective fashion before it can become clinically useful.

Battagli (Battagli et al., Cancer Research Vol. 63 December 15, 2003) teaches that hypermethylation of VHL genes was observed only in clear cell renal cancer (page 8697, column 1, paragraph 1). Battagli teaches that p14 and APC are more common in non nuclear cell cancers (page 8697, column 1, paragraph continued from previous page). Therefore the art teaches that the methylation of one gene is not sufficient to detect any type of kidney cancer, and thereby suggests that one gene is not sufficient to detect all cancers.

With regard to p16 methylation and gastric cancer, Waki (Waki, et al. American Journal of Pathology, 8/2/02; 161:399-403) teaches that methylation of p16 was present

in both neoplastic and nonneoplastic gastric epithelia (pg 400, col 2, para 1). Waki teaches that ruling out the use of p16 methylation as a marker for risk of developing gastric cancer due to the high frequencies of p16 methylation in nonneoplastic gastric carcinomas (pg 403, col 1, para 1).

Regarding p16 methylation in other organisms, Bai (Bai, et al. Mutation Research 2003; 535:73–78) teaches that p16 promoter hypermethylation was observed during the process of neoplastic progression in rat gastric carcinoma (pg 77, col 1, para 2). Patel (Patel, et al. Carcinogenesis. 2000 Sep;21(9):1691-700) teaches analyzing primary mouse lung tumors for p16 methylation status (pg 1691, col 2, para 3) by performing bisulfite genomic sequencing (pg 1692, col 2, para 2).

Quantity of Experimentation

Claims 1-3 are broadly drawn to a method of in vitro detection of malignant potential of dysplasia comprising extracting genomic DNA from any sample, detecting the methylation state of p16 CpG islands in genomic DNA by amplification; and determining malignant potential of any sample based upon the presence of methylated p16 CpG. The specification does not provide any definition of what constitutes malignant potential. The term "malignant potential" seems to indicate a numeric probability, however, the specification does not provide any numeric values associated with the term, and therefore it is unclear and unpredictable to use a determination of methylation status of a gene as a means of detecting malignant potential.

Claims 1-3 are broadly drawn to a method of in vitro detection of malignant potential of dysplasia comprising extracting genomic DNA from any sample, detecting

the methylation state of p16 CpG islands in genomic DNA by amplification; and determining malignant potential of any sample based upon the presence of methylated p16 CpG. The specification and Sun teach performing the study in humans, but neither study provides any data from non-human organisms. Bai and Patel teach that p16 methylation is observed in some mouse and rat cancers. However, Das and Battagli teach that gene methylation that is associated with one type of cancer is not necessarily associated with other types of cancer. Therefore, the skilled artisan would be required to perform a large study to determine if aberrant p16 methylation can be used in organisms other than humans, mice and rats as a means of detecting malignant potential of dysplasia, and the skilled artisan would be required to determine for which cancers the p16 methylation is predictive. This would require undue and unpredictable experimentation with no expectation of success.

Claims 1-3 are broadly drawn to a method of in vitro detection of malignant potential of dysplasia comprising extracting genomic DNA from any sample, detecting the methylation state of p16 CpG islands in genomic DNA by amplification; and determining malignant potential of any sample based upon the presence of methylated p16 CpG. While the art (see above discussion of Bai, Wong and Belinsky) teaches several examples of studying p16 methylation in cancer, the specification and Sun teach that aberrant hypermethylation was only predictive of ~24% of cases that progressed to gastric carcinoma. This is not a significant result. Das and Battagli teach that gene methylation that is associated with one type of cancer is not necessarily associated with other types of cancer. Sun teaches that aberrant p16 methylation was

reported as being unable to predict the evolution of precancerous bronchial lesions in a 2 year follow-up. Wang teaches that p16 methylation is not a marker for risk of developing gastric carcinoma. Therefore, the skilled artisan would be required to perform a large study in order to determine if aberrant p16 methylation can be used to detect malignant potential of dysplasia in gastric tissue or in other tissues. This would require undue and unpredictable experimentation with no likelihood of success.

Conclusion

Given the lack of data from all organisms, the lack of significant data from gastric tissue, the lack of definition for malignant potential, and the lack of study from other tissues, a method of in vitro detection of malignant potential of dysplasia comprising extracting genomic DNA from any sample, detecting the methylation state of p16 CpG islands in genomic DNA by amplification; and determining malignant potential of any sample based upon the presence of methylated p16 CpG is replete with unpredictable experimentation that is considered undue.

Thus given the broad claims in an art whose nature is unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the methods of the claims as broadly written.

Claim Rejections - 35 USC § 102

1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

2. It is noted that while there is a total lack of enablement set forth for claims 1-3, the following art rejections are also applied because the claims broadly read on detecting cancer in a sample. Furthermore, the limitation "detecting a malignant potential of dysplasia" has not been given any weight for the purpose of the art rejections.

3. Claims 1-3 are rejected under 35 U.S.C. 102(b) as being anticipated by Wong (Wong, et al. Cancer Research, January 1, 1999; 59;71–73).

Regarding claims 1 and 2, Wong teaches detecting p16 methylation in the plasma or serum of HCC (hepatocellular carcinoma) patients (pg 71, col 1, introduction). Wong teaches that DNA was extracted from plasma samples (pg 71, col 2, para 1), and that p16 methylation was determined by MSP (methylation specific PCR) (pg 71, col 1 introduction and col 2, para 3-6). Wong teaches that a significant proportion of HCC patients were show to have aberrant p16 methylation in plasma.

Regarding claim 3, Wong teaches primers used for MSP (pg 79, col 2, para 4). Since the primers 59-TTATTAGAGGGTGGGGCGGATCGC-39 and 59-GACCCCGAACCGCGACCGTAA-39, both contain a "G", for example, they are complimentary to "any part of" SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, or SEQ ID NO:4, as is required by the claim.

Therefore all limitations of these claims have been taught by the reference.

4. Claims 1-3 are rejected under 35 U.S.C. 102(b) as being anticipated by Bai (Bai, et al. Mutation Research 2003; 535:73-78).

Regarding claims 1 and 2, Bai teaches that p16 promoter hypermethylation was observed during the process of neoplastic progression in rat gastric carcinoma (pg 77, col 1, para 2). Bai teaches that analysis of p16 was performed by subjecting genomic DNA to Methylation specific PCR (pg 77, col 2, para 2-3).

Regarding claim 3, Bai teaches using, for example, the primers sense 5'-AAT TCG AGG AGA GCG ATT CG-3', antisense 5'-ACC TAT ATC GAA ATA CGA CCG A-3'. Since both primers contain a "G", for example, they are complimentary to "any part of" SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, or SEQ ID NO:4, as is required by the claim.

Therefore, all limitations of the claims have been taught by the reference.

5. Claims 1-3 are rejected under 35 U.S.C. 102(e) as being anticipated by Belinsky (Belinsky, et al. US PGPub 20040038245, published 2/26/04, priority date 8/25/00).

Belinsky teaches a molecular marker-based method for monitoring and detecting

cancer in humans by detecting the aberrant methylation of the p16 gene from sputum samples (abstract).

Regarding claims 1 and 2, Belinsky teaches that DNA was extracted from tissue samples (pg 4, para 40) and subjected to a modified MSP (methylation specific PCR) procedure (pg 4, para 41). Belinsky teaches that p16 aberrant methylation was detected in 48% of patients with Squamous Cell Carcinoma (SCC)

It is noted that since the DNA was isolated from tissues, it is considered to be encompassed by the recitation of "genomic DNA". It is also noted that for purposes of this rejection, detection of aberrant p16 in patients with SCC is considered to be broadly encompassed by the recitation of "determination of malignant potential".

Regarding claim 3, Belinsky teaches using primers specific for methylated or unmethylated template, specifically, a p16 primer with SEQ ID NO:3 (pg 4, para 42). SEQ ID NO:3 of Belinsky aligns with a part of SEQ ID NO: 1 in the instant application (See alignment).

Sequence alignment

Qy = instant SEQ ID NO: 1, Db = Belinsky SEQ ID NO: 3

```
Qy        242 GATUUAGGTGGGTAGAGGGTUTGU 265
              |||::|||||||||||||||:||:
Db         24 GATTTAGGTGGGTAGAGGGTTTGT 1
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Therefore all limitations of these claims have been taught by the reference

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jaime M. Greene whose telephone number is 571-270-3052. The examiner can normally be reached on Monday-Thursday, 7:30am-5:00pm, ALT. Friday, EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Jaime M. Greene

Jaime M. Greene 12/17/07

RAM R. SHUKLA, PH.D.
SUPERVISORY PATENT EXAMINER